Scholars Journal of Applied Medical Sciences (SJAMS) ISSN 2320-6691 (Online)
Sch. J. App. Med. Sci., 2014; 2(1B):185-192 ISSN 2347-954X (Print)

(An International Publisher for Academic and Scientific Resources)
www.saspublishers.com DOI: 10.36347/sjams.2014.v02i01.0039

Research Article

A Research on Autoimmunity in the Cases with Epilepsy or Febrile Convulsion

Eray Basman[1], Mustafa Aydin[2]*, Nimet Kabakus[1], Esra Kocoglu[3], Seyda Ozsoy[3], Aysu Kiyan[4]
[1]Department of Pediatric Neurology, Faculty of Medicine, Abant Izzet Baysal University, 14280, Bolu, Turkey
[2]Division of Neonatology, Department of Pediatrics, Elazig Training and Research Hospital, 23000, Elazig, Turkey
[3]Department of Microbiology, Faculty of Medicine, Abant Izzet Baysal University, 14280, Bolu, Turkey
[4]Department of Public Health, Faculty of Medicine, Abant Izzet Baysal University, 14280, Bolu, Turkey

***Corresponding author**
Dr. Mustafa AYDIN
Email: drlmustafa@hotmail.com

Abstract: We aimed to investigate the relationship between the autoimmunity and epileptic paroxysmal disorders. It was a prospective case-control study (Setting: Ambulatory or hospitalized care). A total of 32 patients and 16 healthy children were included in the study. Anti-glutamate- N-methyl-D-aspartate receptor, anti-glutamic acid decarboxylase and anti-ganglioside (GM1, GM2, GM3, GD1a, GD1b, GT1b, and GQ1b) antibodies' levels were evaluated. Overall, anti-ganglioside antibodies were found positive in approximately one third of the patients (11/32, %34.4). The positivity rate was 43.8% (7/16) in the epilepsy group ($p>0.05$) and 25% (4/16) in the febrile convulsions (FC) group ($p>0.05$) while it was 18.8% (3/16) in the control group. In the study group, the mean age of the patients with the autoantibody positivity (36.6±37 months) was significantly lower than the mean age of the patients with the autoantibody negativity (67.9±47.4 months) ($p<0.05$). The mean age of the patients with the autoantibody positivity was also significantly lower (43.7±45.8 months vs. 112±36.5 months) in the epilepsy group ($p<0.05$). In addition, while the electroencephalographic (EEG) abnormality was found significant in all four FC patients with the anti-ganglioside GT1b positivity ($p<0.05$); it was not remarkable in the epilepsy group with the anti-ganglioside positivity ($p>0.05$). It is determined that the autoantibody positivity may be cautionary in terms of the risk of epilepsy development and the persistent EEG abnormality in the patients with the newly diagnosed epilepsy and/or FC; and autoantibodies may become negative with the increased age.
Keywords: Epilepsy, febrile convulsion, anti-ganglioside antibodies, anti-glutamate receptor antibody, anti-glutamic acid decarboxylase antibody, children

INTRODUCTION

It is known for a long time that autoimmunity and targeted autoantibodies may cause different disorders in many tissues as seen in the central nervous system (CNS)[1]. The CNS is known immunologically as a privileged zone and separated from the peripheral circulation by means of the blood-brain barrier. Hence, it is protected from autoantibodies in the serum. However, according to the current studies, the autoimmune etiology is considered as an etiological factor for some CNS disorders such as seizures [2]. It is demonstrated that the antibodies occurred especially against the voltage-dependent calcium and potassium channels (VGCC, VGKC), the glutamate- N-methyl-D-aspartate (NMDA) receptor, the glutamic acid decarboxylase (GAD), and the gliadin are closely associated with CNS disorders[3].

It is considered that recurrent seizures are related to the genetic predisposition and chemo-physiological changes of the neuron and annexes [4]. In addition to other causes, the evidence regarding the role of autoimmune mechanisms as an etiological factor in epileptic seizures is increasing [5]. These evidences include the increased level of some autoantibodies in the serum, the demonstration of these antibodies as an epileptogenic in some experimental studies, and the response of the seizures to immunomodulation [5, 6].

Febrile convulsion (FC) is the most common type of childhood seizures. The genetic predisposition is considered due to the frequent FC history in parents and also siblings. Recently, in addition to the autosomal dominant inheritance, mutations related to FC gene on 19P and 8q13-21 chromosomes were detected in some families [7]. Based on our research, we found a very small number of outdated studies in the literature with the limited data investigating the relationship between the FC and the immune system [8]. Furthermore, we determined that the relationship between the FC and neural tissue-specific antibodies have not been investigated previously. Therefore, we investigated autoantibodies; previously used in the studies those evaluate the autoimmunity of CNS, in order to demonstrate the possible relationship between the induction of paroxysmal convulsions and the

autoimmunity. It was aimed to explore the etiopathogenetic role of autoantibodies on different seizure types in the newly diagnosed epilepsy and FC patients.

MATERIALS AND METHODS

The study was prospectively conducted on children with the newly diagnosed epilepsy and FC at the Child Neurology Clinic of the Abant Izzet Baysal University (AIBU) Medical School between January 2011 and May 2011. Study was approved ethically by the AIBU Faculty of the Medicine Clinical Research Ethics Board with the study no. 2011/10 and also supported by the Rectorship of the AIBU Head of Scientific Research Projects Commission according to the decision no. 2011/51.

Subjects

This study was conducted on selected groups among patients with the newly diagnosed epilepsy and FC who met the following criteria: normal physical and neurological examinations, without any history of the recent drug use, with no history of the trauma and the lack of the evidence of the organisity in the cranial imaging. These groups were consist of patients with the epilepsy (Group I, n=16) and FC (Group II, n=16), and healthy children (Group III, n=16) presented to the healthy children outpatient clinic. During the selection of healthy children, the lack of epilepsy and/or FC history in the child as well as his/her family was also taken into account. Signed informed consent form was obtained from families of patients meeting the study criteria. Following the detailed history and the detailed physical / neurological examinations, laboratory examinations on the etiology of the seizure were conducted. Thus, in addition to routine laboratory tests, routine and activated patient electroencephalographies (EEG) (including sleep) were obtained. While the first EEGs of all patients were obtained within 7 days, the second EEGs of FC patients were repeated 15 days later[9,10]. The patients in Group I were divided into sub-groups with generalized (Group IA) and focal seizures (Group IB), and the patients in Group II were divided into sub-groups with the simple FC (Group IIA) and the complicated (Group IIB) FC. Patients in the control group constituted Group III.

Patients' demographic information, diagnoses, seizures types, the family history about the presence of the epilepsy, and the EEG data were recorded. Blood samples were centrifuged at Heraeus Labofuge 200 Compact Desktop centrifuge device for 4 minutes at 3.500 rpm. The separated serum was transferred to Eppendorf tubes; Eppendorf tubes were stored in the Heraeus Herafreeze freezer at -77 ° C until the day of tests.

Study Method

Examination of anti-ganglioside antibodies

The ganglioside profile 2 Strip (EUROLINK, EUROIMMUN, Lubeck, Germany) study is a test that provides the qualitative detection of IgG antibodies formed in the serum against the ganglioside GM1, GM2, GM3, GD1a, GD1b, GT1b and GQ1b through membrane strips coated with the antigen. It works with the immunoblot method.

The examination of the anti-glutamate receptor antibodies

This study is a test that based on the determination of glutamate receptor (NMDA-type) antibodies (EUROIMMUN, Lubeck, Germany) and the detection of antibodies occurred against glutamate receptors (NMDA type) by indirect immunofluorescence antibody test. The results can be interpreted as qualitative or quantitative.

The examination of anti-GAD antibodies

The purpose of this test was to investigate serum IgG antibodies against GAD (EUROIMMUN, Lubeck, Germany) with the ELISA method.

Statistical Analysis

The statistical analysis was performed by using SPSS (SPSS, version 17.0, SPSS Inc., Chicago, IL, USA). The Chi-square test, the Kruskal-Wallis sequent one-way variance analysis test and the Mann-Whitney U test were used for the evaluation among groups. The data was expressed as the mean ± SD.

RESULTS

The General Characteristics of Groups

The general distribution of groups was given in Table 1. Even though there was not a significant difference in the age of the epilepsy group and the control group (103.19±53.33 months, 82.13±52.66 months respectively, $p > 0.05$); a substantial difference was found between the control group and FC (103.19 ± 53.33 months, 32.13±16.60 months respectively, $p<0.05$). Gender differences were not also found among groups ($p>0.05$, Table 1).

EEG Findings

The family history of FC was significantly higher in FC group (37.5%) than the epilepsy group (12.5%) as expected.

Based on the EEG results, pathological findings were found in the majority of the first EEGs of the epilepsy and FC groups (epilepsy group: 10/16, 62.5% and FC group: 8/16, 50%) while the regression of the EEG abnormality was detected in the second EEGs repeated after two weeks in the FC group (5/16, %31.3). While the non-specific high-voltage sharp-contoured delta waves in the posterior regions were determined as a evidence of the abnormal EEG in the first and the second EEGs of patients with the simple FC (Group IIA); all abnormal EEGs of the complicated

FC (Group IIB) and the epileptic group (Group I) were in the epileptiform character.

Antibody Results

Antibody results of all patients and healthy children were summarized in Table 2 and positive results were summarized in Table 3.

The presence of one or more antibody positivity in patients with the identified abnormal findings in the first EEGs of the epilepsy group (Generalized: 2/10, Focal: 3/6) and in the first and the second EEGs of the FC group (Simple FC: 3/14, complicated: 1/2) was remarkable. The combination of the antibody positivity with the abnormal EEG findings was determined in half of the patients with the complicated FC and the focal epilepsy.

The mean age of the autoantibody positivity identified patients (11/32, 34.3%) (36.6±37 months) was significantly lower than the mean age of the autoantibody negativity identified patients (21/32, 65.6%) (67.9±47.4 months) ($p<0.05$). A similar condition was determined in the epilepsy group (the mean age of the autoantibody-positive patients: 43.7±45.8 months, the mean age of the autoantibody-negative patients: 112±36.5 months, $p<0.05$). Even though a similar result was obtained in the FC group (the mean age of the autoantibody-positive patients: 24.3±8.3 months, the mean age of the autoantibody-negative patients: 34.8±18 months), this was not statistically significant ($p>0.05$). In the control group, contrary to study groups, the mean age of the autoantibody-negative patients (98.4±58.2 months) was lower than the mean age of the autoantibody-positive patients (124±13.9 months), however this was not statistically significant ($p>0.05$).

Following Results Have Been Identified by the Consideration of All Autoantibody Data

- **Anti-ganglioside antibodies**
  - Considering the whole patient group, approximately one third of patients (34.4%, 11/32) were positive for anti-ganglioside antibodies. While this rate was close to 43.8% (7/16) in the epilepsy group, it was determined as 25% (4/16) in the FC group. Even though all these ratios were found high in comparison to the control group (18.8%, 3/16), they were not statistically significant ($p>0.05$).
  - The antibodies against to GM1, GD1a, GD1b and GQ1b were found negative in all groups.
  - The antibody against to GM2: Based on the distribution of results per group; it was determined that all antibody results were negative in the epilepsy group and positive in one patient of each FC and the control group ($p>0.05$). This patient with FC had the simple FC, and there was a family history ($p>0.05$) and an EEG abnormality ($p>0.05$).
  - The antibody against to GM3: Considering the whole patient and the control group, it was positive only in one patient with the epilepsy ($p>0.05$) and all other antibody results of this patient were found negative.
  - The antibody against to GT1b: Higher positivity of this antibody was determined in all groups. While this rate was the highest in the epilepsy group (37.5%, n=6/16, $p>0.05$); it was declining in FC (25%, n=4/16, $p>0.05$) and the control group (18.8%, n=3/16, $p>0.05$). In addition, the EEG abnormality of all four antibody positive patients with FC was significant (simple FC: 3/3, complicated FC: 1/1, $p<0.05$); it was not significant in the epilepsy group (generalized: 2/2, focal: 3/4, $p>0.05$).

- **Anti-glutamate receptor antibodies and anti-GAD antibodies**
  - The results of both of these antibodies were negative in all groups.

Table 1: General distribution of the study and control groups

<table>
<tr><th colspan="4">Grup I
(Epilepsy)</th><th colspan="4">Grup II
(FC)</th><th>Grup III
(Control)</th></tr>
<tr><td colspan="2">Grup IA
(Generalized)
n (%)</td><td colspan="2">Grup IB
(Focal)
n (%)</td><td colspan="2">Grup IIA
(Simple)
n (%)</td><td colspan="2">Grup IIB
(Complicated)
n (%)</td><td rowspan="5">Female: 12 (%75)
Male: 4 (%25)
Total: 16 (%100)
Mean age:
103.19±53.33
(7-192) months</td></tr>
<tr><td colspan="2">10 (%62.5)</td><td colspan="2">6 (%37.5)</td><td colspan="2">14 (%87.5)</td><td colspan="2">2 (%12.5)</td></tr>
<tr><td>Female
7 (70%)</td><td>Male
3 (30%)</td><td>Female
2 (33.3%)</td><td>Male
4 (66.6%)</td><td>Female
5 (35.7%)</td><td>Male
9 (64.2%)</td><td>Female
1 (50%)</td><td>Male
1 (50%)</td></tr>
<tr><td colspan="4">16 (100%)
Mean age: 82.13±52.66 (4-168) months</td><td colspan="4">16 (100%)
Age: 32.13±16.60 months (15-72 months)</td></tr>
<tr><td colspan="8">Total patients (n): 32</td></tr>
<tr><td colspan="9">Total patients (n) + Control group (n): 48</td></tr>
</table>

Table 2: Antibody results of the all cases

Sl. No.	Age (months)	Gender	Diagnosis	Anti-gangliozid antibodies							Anti-glutamate receptor antibodies	Anti-GAD antibodies
				GM1	GM2	GM3	GD1a	GD1b	GT1b	GQ1b		
1	36	M	Simple FC	-	-	-	-	-	(+)	-	-	-
2	72	M	Generalized Epilepsy	-	-	-	-	-	-	-	-	-
3	4	F	Focal Epilepsy	-	-	-	-	-	(+)	-	-	-
4	15	F	Simple FC	-	-	-	-	-	-	-	-	-
5	120	F	Focal Epilepsy	-	-	-	-	-	-	-	-	-
6	108	F	Generalized Epilepsy	-	-	-	-	-	-	-	-	-
7	17	F	Simple FC	-	(+)	-	-	-	(+)	-	-	-
8	132	F	Generalized Epilepsy	-	-	-	-	-	-	-	-	-
9	48	M	Focal Epilepsy	-	-	-	-	-	-	-	-	-
10	19	M	Simple FC	-	-	-	-	-	-	-	-	-
11	96	F	Generalized Epilepsy	-	-	-	-	-	-	-	-	-
12	8	M	Focal Epilepsy	-	-	-	-	-	(+)	-	-	-
13	23	F	Simple FC	-	-	-	-	-	-	-	-	-
14	120	F	Generalized Epilepsy	-	-	-	-	-	-	-	-	-
15	24	M	Simple FC	-	-	-	-	-	(+)	-	-	-
16	30	M	Simple FC	-	-	-	-	-	-	-	-	-
17	20	F	Complicated FC	-	-	-	-	-	(+)	-	-	-
18	108	M	Focal Epilepsy	-	-	-	-	-	(+)	-	-	-
19	28	F	Simple FC	-	-	-	-	-	-	-	-	-
20	96	M	Generalized Epilepsy	-	-	(+)	-	-	-	-	-	-
21	144	F	Generalized Epilepsy	-	-	-	-	-	-	-	-	-
22	14	F	Generalized Epilepsy	-	-	-	-	-	(+)	-	-	-
23	69	M	Focal Epilepsy	-	-	-	-	-	(+)	-	-	-
24	168	M	Generalized Epilepsy	-	-	-	-	-	-	-	-	-
25	33	M	Simple FC	-	-	-	-	-	-	-	-	-
26	48	M	Simple FC	-	-	-	-	-	-	-	-	-
27	24	M	Simple FC	-	-	-	-	-	-	-	-	-
28	7	F	Generalized Epilepsy	-	-	-	-	-	(+)	-	-	-
29	18	M	Simple FC	-	-	-	-	-	-	-	-	-
30	47	F	Simple FC	-	-	-	-	-	-	-	-	-
31	60	M	Simple FC	-	-	-	-	-	-	-	-	-
32	72	M	Complicated FC	-	-	-	-	-	-	-	-	-
33	156	F	Control	-	-	-	-	-	-	-	-	-
34	132	M	Control	-	-	-	-	-	(+)	-	-	-
35	36	F	Control	-	-	-	-	-	-	-	-	-
36	192	F	Control	-	-	-	-	-	-	-	-	-
37	108	M	Control	-	-	-	-	-	-	-	-	-
38	144	F	Control	-	-	-	-	-	-	-	-	-
39	168	F	Control	-	-	-	-	-	-	-	-	-
40	72	F	Control	-	-	-	-	-	-	-	-	-
41	132	M	Control	-	(+)	-	-	-	(+)	-	-	-
42	108	F	Control	-	-	-	-	-	(+)	-	-	-
43	48	F	Control	-	-	-	-	-	-	-	-	-
44	7	M	Control	-	-	-	-	-	-	-	-	-
45	144	F	Control	-	-	-	-	-	-	-	-	-
46	96	F	Control	-	-	-	-	-	-	-	-	-
47	48	F	Control	-	-	-	-	-	-	-	-	-
48	60	F	Control	-	-	-	-	-	-	-	-	-

Table 3: The cases with positive antibody results and EEG abnormalities

Sl. No.	Age (months)	Gender	Diagnosis	Family history	EEG findings	Anti-gangliozid antibodies		
						GM2	GM3	GT1b
1	36	M	Simple FC	-	(+) / (+)*	-	-	(+)
3	4	F	Focal Epilepsy	-	(+)	-	-	(+)
7	17	F	Simple FC	(+)	(+) / (+)*	(+)	-	(+)
12	8	M	Focal Epilepsy	-	-	-	-	(+)
15	24	M	Simple FC	-	(+) / (+)*	-	-	(+)
17	20	F	Complicated FC	(+)	(+) / (+)*	-	-	(+)
18	108	M	Focal Epilepsy	(+)	(+)	-	-	(+)
20	96	M	Generalized Epilepsy	-	-	-	(+)	-
22	14	F	Generalized Epilepsy	-	(+)	-	-	(+)
23	69	M	Focal Epilepsy	-	(+)	-	-	(+)
28	7	F	Generalized Epilepsy	-	(+)	-	-	(+)
34	132	M	Control			-	-	(+)
41	132	M	Control			(+)	-	(+)
42	108	F	Control			-	-	(+)

EEG: Electroencephalography; *: Second EEG

DISCUSSION

The number of studies investigating the relationship between the epilepsy and the autoimmunity is increasing. Although there was no study about autoantibodies on patients with FC, few studies were related to immunity [8, 11]. In these studies, low levels of immunoglobulins in patients with the epilepsy and FC were shown. Bouma reported the reduction of IgA up to 25% in epileptic patients [12]; Caksen *et al.* identified the low level of the immunoglobulin subgroup in patients with FC and they suggested that FC-related infections may have an important role in the pathogenesis of FC [11]. We think that our study is the first one investigating the etiology of the autoimmunity in patients with FC and therefore it is considered important.

Considering the mean age in the groups, we found the mean age of our patients with FC was lower than patients with the epilepsy. This finding was consistent with the literature [13]. The high family history of the FC group (37.5%) could be explained with the relationship of this disorder with the dominant genetic etiology. Indeed, studies reported that FC genetic dominance rates could increase up to 32% [14].

Based on the abnormal EEG findings in our patients, while the nonspecific abnormal discharges were determined in all patients with the simple FC, the epileptiform characterized discharges were detected in patients with the complicated FC and epilepsy groups. This might indicate that complicated FC patients are very risky in terms of the inclusion of epileptic discharges [10, 15]. It is reported also in a study conducted by Yucel *et al*. that the EEG disorder might be in the important part of these patients and this condition might be together with the epilepsy [15].

Antibodies used in this study occupy an important place in the multi-faceted researches in relation to the CNS [16]. Comments on the positivity of these antibodies in patients with the epilepsy are increasing. In a study conducted by Bartolomei et al, the anti-ganglioside GM1 was positive in a minority of 64 patients (4/64, 6.3%) with the epilepsy [17]. The intravenous immunoglobulin (IVIG) therapy of two patients was useful in the same study and this has been considered as significant. The antibody positivity ratio (1.04%, 1/96) was found smaller in proportion to control groups (4%, 1/25) in the study of Aykutlu et al that was conducted with the juvenile myoclonic epilepsy patients [18]. The lack of the anti-ganglioside GM1 positivity in our patients with the epilepsy demonstrated compatibility with the literature, and also could be explained by the absence of patients with the long follow-up and the resistant epilepsy.

Although it might be considered that the presence of the anti-ganglioside GM2 and anti-ganglioside GM3 positivity only in one FC patient and one epileptic patient was associated with the generalized neurological dysfunction; its positivity also in one patient of the control group made the interpretation of our data difficult. Indeed, it has been reported that these autoantibodies could be associated with neurodegenerative diseases mostly.

GQ1b ganglioside antibodies were reported to be associated with neurological diseases other than the epilepsy [19-21]. It was shown that these antibodies could be responsible for some ataxic ophthalmoplegic cases, Guillain–Barré syndrome and Miller-Fisher syndromes [19]. GQ1b has been reported to be important on the learning function by the interaction with the NMDA receptor way in the hippocampus in the animal studies [20] and also an increase in the intracellular amount of GQ1b after seizures have been reported. Although there were thoughts that it could be associated with the epilepsy [21], it has not been studied enough specifically on patients with the epilepsy. We, therefore, included our patient group into this antibody study, but we were unable to determine a positive result.

Anti-ganglioside antibodies, particularly anti-ganglioside GT1b, were determined to be positive for a significant proportion of our patients. The GT1b antibody positivity, insistent non-specific EEG abnormalities of our patient and togetherness of them in terms of epileptiform discharges were found interesting. Especially in the FC group, togetherness of this antibody with the EEG abnormality was found statistically significant and this might indicate a high rate of EEG abnormalities in GT1b antibody determined patients with FC.

In animal models of De Freitas *et al.* [22] and studies of Izumi *et al.* regarding the samples of the cerebrospinal fluid of patients with West syndrome [23], levels of GT1b were found significantly lower in models with seizures. This finding could be interpreted as the low emergence of the GT1b antigen as a result of blockading with identical antibody and suggested that anti-GT1b is positive. This situation could be considered as compatible with our patient population. However in spite of this, we could not find any study group with the epilepsy or FC that was comparable with our anti-GT1b results.

The presence of the autoantibody positivity in the children of the study and the control group showed the potential production of a generalized autoantibody against CNS. We think that these antibodies may not always result in neuropathological event considering the normal children and normal EEGs in the control group. However, it is clear that this situation needs to be monitored prospectively. On the other size, the determination of the autoantibody positivity in patients with the focal epilepsy and the complicated FC suggests that the autoimmunity can create the focal neuropathological focuses via the autoantibody. Indeed, it is known that the autoimmunity can constitute the focal neuropathological focuses in many autoimmune diseases which are considered as neurological diseases (such as acute disseminated encephalomyelitis, ADEM; multiple sclerosis, MS; Pediatric autoimmune neuropsychiatric diseases, Sydenham's chorea and PANDAS).

Glutamate-NMDA receptors are the receptors that have high calcium permeability and play an important role in the biology of the advanced organisms. They are so effective in cognitive functions such as the development of the central nervous system, the regulation of the breathing and the movement, the learning and the memory. Therefore, disorders and fluctuations in these receptor's functions can cause major problems. It is an area of interest particularly in the treatment of diseases such as stroke, hypoxia, ischemia, head trauma, Huntington's disease, Parkinson's disease, Alzheimer's disease, epilepsy, neuropathic pain, alcoholism, schizophrenia and mood disorders [24]. In a study conducted by Ganor et al regarding the anti-glutamate receptor antibodies, the anti-glutamate / NMDA-receptor antibody positivity was found in 18% of 82 epileptic patients. Especially, the plurality of the diagnosis of the partial epilepsy among these patients attracts attention [6]. In a study conducted by Dambinova *et al.*, it was shown that the level of the glutamate antibody in the blood of patients with the drug-resistant epilepsy was significantly higher than the control group [25]. The absence of the refractory epilepsy patient in our study group can be considered compatible with our negative results of the glutamate receptor antibodies.

There are numerous recent publications in the literature regarding GAD antibodies. GAD is the rate-limiting enzyme of the GABA which is the most important inhibitory neurotransmitter in the CNS. It is synthesized especially in the GABAergic neurons and the pancreas. This antibody can also be used as a screening test of Type 1 diabetes. It is shown to be positive in 80% of patients with the newly diagnosed Type 1 diabetes [26]. Saiz *et al.* showed that there is a neurological disorder in 47 of 61 patients with the positive antibody. The diagnosis was epilepsy in four of these patients and there was hippocampal sclerosis in three patients. The drug resistance was also available in two patients [27]. Anti-GAD antibodies were shown to be positive in 0.4% of the normal population [28]. In a study of Errichiello et al conducted on 233 patients with focal and generalized seizures, a positivity rate of 2.6% was found especially in patients with the cryptogenic temporal lobe epilepsy [29].

The anti-GAD antibody was detected positive in 5.4% of 74 epileptic patients in the study of Verrotti *et al.*, however this rate was insignificant compared with the control group [30]. In a study conducted by Aykutlu *et al.* in Turkey, 96 juvenile myoclonic epilepsy patients were screened and the anti-GAD antibody positivity was found only in 5.8% of patients and it was closer to the ratio in the control group (4%) [18]. The absence of positive result in our patient and control groups could be explained with that our selected epilepsy and FC patients were first diagnosed and did not have severe neuropathological processes yet, and there was not a genetic predisposition in our control group.

There were studies detected the high antinuclear antibody (ANA), anticardiolipin (aCL) and antiphospholipid antibody positivity in the chronic epilepsy and the newly diagnosed epilepsy [31, 32]. Regardless of the type of the epilepsy, ANA positivity was found at a rate of 25% (41/63) among 163 patients with the epilepsy in a study of Verrot *et al.* [31]. Cimaz *et al.* screened 142 patients for aCL, antib2 glycoprotein I (antib2GPI), and anti-prothrombin (aPT). It was shown in this study that aCL, antib2GPI and aPT could be associated with the epilepsy in the children. Being aPT significantly higher especially in young children

could suggest the use of alternative treatment methods for the resistant and difficult cases if these antibodies were detected (antiplatelet therapy). Also in this study, it was shown that there were test positivity in 41 patients (aCL: 15, antib2GPI: 25, aPT: 18, there were more than one positive test in 17 patients). It has been seen that the mean age of the patients with the test positivity was smaller [32]. In our study, we also found in general that the mean age of the patients with positive tests (43.7±45.8) was significantly smaller than the average age of the patients with negative tests (112±36.5 months). This trend was determined in FC patients even though it was not significantly higher (positive: 24.3 ± 8.3 months vs. negative: 34.8 ± 18 months). This might suggest the togetherness of the neural autoantibody pathogenicity with an early age.

In the light of the obtained results, it was determined that autoantibody positivity in patients with the newly diagnosed epilepsy and FC:

- could be a triggering cause in the first epileptic seizures and FC,
- could show togetherness with the risk of the epilepsy and the chronic EEG disorder,
- having a small age in the patient group could be significant in terms of the autoantibody positivity.

If these data were supported with multidirectional studies, and the autoantibody, the epilepsy and the FC relationships could be clarified, then it could be considered that immunomodulatory therapies could be used effectively.

REFERENCES

1. Lernmark A; Autoimmune diseases: are markers ready for prediction? J Clin Invest., 2001; 108:1091-1096.
2. Irani S, Lang B; Autoantibody-mediated disorders of the central nervous system. Autoimmunity, 2008; 41: 55-65.
3. Lang B, Dale RC, Vincent A; New autoantibody mediated disorders of the central nervous system. Curr Opin Neurol., 2003; 16: 351-357.
4. Menkes JH, Sarnat HB, Maria BL; Child Neurology. 7th edition, Philadelphia: Lippincott Williams & Wilkins; 2006.
5. Palace J, Lang B; Epilepsy: an autoimmune disease? J Neurol Neurosurg Psychiatry, 2000; 69:711-714.
6. Ganor Y, Goldberg-Stern H, Lerman-Sagie T, Teichberg VI, Levite M; Autoimmune epilepsy: distinct subpopulations of epilepsy patients harbor serum autoantibodies to either glutamate/AMPA receptor GluR3, glutamate/NMDA receptor subunit NR2A or double-stranded DNA. Epilepsy Res., 2005; 65:11-22.
7. Johnson MV; Seizures in childhood. In Kliegman RM, Behrman RE, Jenson HB, Stanton BF editors; Nelson Textbook of Pediatrics. Principles and Practice. 18th edition, Philadelphia: Saunders Elsevier; 2007: 2457.
8. Montelli TC, Soares AM, Parise-Fortes MR, Rezkallah-Iwasso MT, Padula NM, Peraçoli MT; Alterations of cell-mediated immune response in children with febrile seizures. Arq Neuropsiquiatr., 1997; 55:193-198.
9. Joshi C, Wawrykow T, Patrick J, Prasad A; Do clinical variables predict an abnormal EEG in patients with complex febrile seizures? Seizure, 2005; 14: 429-434.
10. Yücel O, Aka S, Yazicioglu L, Ceran O; Role of early EEG and neuroimaging in determination of prognosis in children with complex febrile seizure. Pediatr Int., 2004; 46: 463-467.
11. Caksen H, Oner AF, Arslan S, Kan MC, Cesur Y, Uner A; Immunoglobulin subgroups in children with febrile seizures. Pediatr Int., 2001; 43: 58-60.
12. Bouma PA; Determining the prognosis of childhood epilepsies by establishing immune abnormalities. Clin Neurol Neurosurg., 1992; 94 Suppl: S54-56.
13. Ellenberg JH, Hirtz DG, Nelson KB; Age at onset of seizures in young children. Ann Neurol., 1984; 15: 127-134.
14. Nuhoğlu Ç, Aka S, Türkmen A, Karatoprak N, Karatoprak N, Özgüner A; Family history in febrile seizures and epileptic seizures. J Kartal Tr., 2002; 13:153-155.
15. Verity CM, Golding J; Risk of epilepsy after febrile convulsions: a national cohort study. BMJ, 1991; 303:1373-1376.
16. Vincent A, Bien CG, Irani SR, Waters P; Autoantibodies associated with diseases of the CNS: new developments and future challenges. Lancet Neurol., 2011; 10:759-772.
17. Bartolomei F, Boucraut J, Barrié M, Kok J, Dravet C, Viallat D *et al.*; Cryptogenic partial epilepsies with anti-GM1 antibodies: a new form of immune-mediated epilepsy? Epilepsia, 1996; 37: 922-926.
18. Aykutlu E, Baykan B, Gürses C, Gokyigit A, Saruhan-Direskeneli G; No association of anti-GM1 and anti-GAD antibodies with juvenile myoclonic epilepsy: a pilot study. Seizure, 2005; 14: 362-366.
19. Kusunoki S, Chiba A, Kanazawa I; Anti-GQ1b IgG antibody is associated with ataxia as well as ophthalmoplegia. Muscle Nerve, 1999; 22: 1071-1074.
20. Jung WR, Kim HG, Shin MK, Park DI, Kim KL; The effects of ganglioside GQ1b on the NMDA receptor signaling pathway in H19-7 cells and rat hippocampus. Neuroscience, 2010; 165:159-167.

21. Kato K, Iwamori M, Hirabayashi Y; Increase of GQ1b in the hippocampus of mice following kindled-seizures. Neurosci Lett., 2008; 441: 286-290.
22. de Freitas RM, do Nascimento KG, Ferreira PM, Jordán J; Neurochemical changes on oxidative stress in rat hippocampus during acute phase of pilocarpine-induced seizures. Pharmacol Biochem Behav., 2010; 94: 341-345.
23. Izumi T, Ogawa T, Koizumi H, Fukuyama Y; Low levels of CSF gangliotetraose-series gangliosides in West syndrome: implication of brain maturation disturbance. Pediatr Neurol., 1993; 9: 293-296.
24. Van Dongen AM; Biology of the NMDA Receptor. Frontiers in Neuroscience. Boca Raton (FL): CRC Press; 2009.
25. Dambinova SA, Izykenova GA, Burov SV, Grigorenko EV, Gromov SA; The presence of autoantibodies to N-terminus domain of GluR1 subunit of AMPA receptor in the blood serum of patients with epilepsy. J Neurol Sci., 1997; 152: 93-97.
26. Solimena M, De Camilli P; Autoimmunity to glutamic acid decarboxylase (GAD) in Stiff-Man syndrome and insulin-dependent diabetes mellitus. Trends Neurosci., 1991; 14: 452-457.
27. Saiz A, Blanco Y, Sabater L, González F, Bataller L, Casamitjana R *et al.*; Spectrum of neurological syndromes associated with glutamic acid decarboxylase antibodies: diagnostic clues for this association. Brain, 2008; 131: 2553-2563.
28. Batstra MR, Petersen JS, Bruining GJ, Grobbee DE, de Man SA, Molenaar JL *et al.*; Low prevalence of GAD and IA2 antibodies in schoolchildren from a village in the southwestern section of the Netherlands. Hum Immunol., 2001; 62:1106-1110.
29. Errichiello L, Perruolo G, Pascarella A, Formisano P, Minetti C, Striano S *et al.*; Autoantibodies to glutamic acid decarboxylase (GAD) in focal and generalized epilepsy: A study on 233 patients. J Neuroimmunol., 2009; 211:120-123.
30. Verrotti A, Greco R, Altobelli E, Latini G, Morgese G, Chiarelli F; Anticardiolipin, glutamic acid decarboxylase, and antinuclear antibodies in epileptic patients. Clin Exp Med., 2003; 3: 32-36.
31. Verrot D, San-Marco M, Dravet C, Genton P, Disdier P, Bolla G *et al.*; Prevalence and signification of antinuclear and anticardiolipin antibodies in patients with epilepsy. Am J Med., 1997; 103: 33-37.
32. Cimaz R, Romeo A, Scarano A, Avcin T, Viri M, Veggiotti P *et al.*; Prevalence of anti-cardiolipin, anti-beta2 glycoprotein I, and anti-prothrombin antibodies in young patients with epilepsy. Epilepsia, 2002; 43: 52-59.